



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Christian P. Larsen et al. **Examiner:** Not yet known
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Filed: January 25, 2002 **Docket No.:** D0136NP/30436.5
Title: METHODS OF INDUCING ORGAN TRANSPLANT TOLERANCE AND
CORRECTING HEMOGLOBINOPATHIES

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CERTIFICATE UNDER 37 CFR 1.8:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on July 31, 2002.

Renato Marco P. Domingo
By: Renato Marco P. Domingo

INFORMATION DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b)(3))

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner. They are as follows:

- U.S. Patent No. 4,603,102 issued July 29, 1986 – **Exhibit 1**
- U.S. Patent No. 5,430,057 issued July 4, 1995 – **Exhibit 2**
- U.S. Patent No. 5,434,131 issued July 18, 1995 – **Exhibit 3**
- U.S. Patent No. 5,559,148 issued September 24, 1996 – **Exhibit 4**
- U.S. Patent No. 5,637,481 issued June 10, 1997 – **Exhibit 5**
- U.S. Patent No. 5,773,253 issued June 30, 1998 – **Exhibit 6**
- U.S. Patent No. 5,844,095 issued December 1, 1998 – **Exhibit 7**
- U.S. Patent No. 5,851,795 issued December 22, 1998 – **Exhibit 8**
- U.S. Patent No. 5,876,692 issued March 2, 1999 – **Exhibit 9**
- U.S. Patent No. 5,885,579 issued March 23, 1999 – **Exhibit 10**
- U.S. Patent No. 5,885,796 issued March 23, 1999 – **Exhibit 11**

- U.S. Patent No. 6,090,914 issued July 18, 2000 – **Exhibit 12**
- U.S. Patent No. 6,113,898 issued September 5, 2000 – **Exhibit 13**
- U.S. Patent No. 6,217,867 B1 issued April 17, 2001 – **Exhibit 14**
- International Publication No. WO96/23071 published August 1, 1996 – **Exhibit 15**
- Abrams, Judith R. et al., “Blockade of T Lymphocyte Costimulation with Cytotoxic T Lymphocyte- associated Antigen 4-Immunoglobulin (CTLA4Ig) Reverse the Cellular Pathology of Psoriatic plaques, Including the Activation of Keratinocytes, Dendritic Cells, and Endothelial Cells,” *Journal of Experimental Medicine*, 2000, 192:681-693 – **Exhibit 16**
- Adams, Andrew B. et al., “Costimulation Blockade, Busulfan, and Bone Marrow Promote Titratable Macrochimerism, Induce Transplantation Tolerance, and Correct Genetic Hemoglobinopathies with Minimal Myelosuppression,” *Journal of Immunology*, 2001, 167:1103-11 – **Exhibit 17**
- Ahmed, Rafi et al., “Selection of Genetic Variants of Lymphocytic Choriomeningitis Virus in Spleens of Persistently Infected Mice,” *Journal of Experimental Medicine*, 1984, 160:521-40 – **Exhibit 18**
- Andreasen, Susanne Ørding et al., “Surface marker abnormalities in myelodysplastic syndromes,” *Journal of Immunology*, 2000, 164:3689-97 – **Exhibit 19**
- Aruffo, S., Presentation of “Approaches to Immune Regulation” at BIO 2000 in Boston, Massachusetts, March 27, 2000 – **Exhibit 20**
- Basch, Ross S. et al., “Growth of Human Hematopoietic Cells in Immunodeficient Mice Conditioned with Cyclophosphamide and Busulfan,” *Stem Cells*, 1997, 15:314-23 – **Exhibit 21**
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- Larsen, Christian P. et al., Abstract of "Prolongation of Renal Allograft Survival with Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-IG Fusion Protein In Non-Human Primates," in *Transplantation*, 2000, 69:S123, #45 – **Exhibit 62**
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- Swerlick, Robert A. et al., " $\alpha_4\beta_1$ -Integrin Expression on Sickle Reticulocytes: Vascular Cell Adhesion Molecule-1-Dependent Binding to Endothelium," *Blood*, 1993, 82:1891-9 – **Exhibit 105**
- Sykes, Megan et al., "Induction of high levels of allogeneic hematopoietic reconstitution and donor-specific tolerance without myelosuppressive conditioning," *Nature Medicine*, 1997, 3:783-7 – **Exhibit 106**
- Thomas, E. Donnall et al., "Marrow Transplantation for Thalassaemia," *The Lancet*, 1982, 2:227-9 – **Exhibit 107**
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- Vermylen, C. et al., "Haematopoietic stem cell transplantation for sickle cell anaemia: the first 50 patients transplanted in Belgium," *Bone Marrow Transplantation*, 1998, 22:1-6 – **Exhibit 113**
- Walters, Mark C. et al., "Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report," *Blood*, 2000, 95:1918-24 – **Exhibit 114**
- Warner, G. L. et al., Abstract and Presentation of "Bioactivity of BMS-188667 (CTLA4Ig) in Cynomolgus Monkeys," in Seattle, Washington, March 16-22, 1995 – **Exhibit 115**
- Webb, Louise M. C. et al., "Prevention and amelioration of collagen-induced arthritis by blockade of the CD28 co-stimulatory pathway: requirement for both B7-1 and B7-2" *European Journal of Immunology*, 1996, 26:2320-8 – **Exhibit 116**
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- Weiner, R. et al., Abstract and Presentation of "Validation and PK Application of a Double Antibody Sandwich Enzyme Immunoassay For the Quantitation of Human CTLA4Ig Fusion Protein (BMS-188667) in Mouse Serum," November 6-10, 1994 – **Exhibit 118**
- Weiner, Russell et al., Abstract and Presentation of "Validation of an Enzyme Immunoassay for the Quantitation of Human CTLA4Ig Fusion Protein in Human Serum," in Miami, Florida, November 1995 – **Exhibit 119**
- Weiner, Russell, Abstract and Presentation of "Automation and Validation of An EIA For Quantitation of Human CTLA4Ig in Monkey Serum," in Miami, Florida, November 1995 – **Exhibit 120**

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- Weiner, Russell S., Abstract and Presentation of "Industrial Perspectives of Primary Analytical Tools for Macromolecules- Principles and Applications with Examples" March 1, 2000 – **Exhibit 122**
- Wekerle, Thomas et al., "Extrathymic T Cell Deletion and Allogeneic Stem Cell Engraftment Induced with Costimulatory Blockade Is Followed by Central T Cell Tolerance," *Journal of Experimental Medicine*, 1998, 187:2037-44 – **Exhibit 123**
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- Wells, Andrew D. et al., "Following the Fate of Individual T Cells throughout Activation and Clonal Expansion," *Journal of Clinical Investigation*, 100:3173-83 – **Exhibit 125**
- Welsh, Raymond M. et al., "Virus-Induced Abrogation of Transplantation Tolerance Induced by Donor-Specific Transfusion and Anti-CD154 Antibody," *Journal of Virology*, 2000, 74:2210-8 – **Exhibit 126**
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- Yang, Hyekyung et al., "Virus-Induced Polyclonal Cytotoxic T Lymphocyte Stimulation," *Journal of Immunology*, 1989, 142:1710-8 – **Exhibit 133**
- Yeager, A. M. et al., "Growth retardation and depigmentation of hair after high-dose busulfan and congenic hemtopoietic cell transplantation in mice," *Bone Marrow Transplantation*, 1992, 9:199-204 – **Exhibit 134**
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- Zarozinski, Christopher C. and Raymond M. Welsh, "Minimal Bystander Activation of CD8 T Cells during the Virus-induced Polyclonal T Cell Response," *Journal of Experimental Medicine*, 1997, 185:1629-39 – **Exhibit 136**

This statement should be considered because it is submitted before the mailing date of the first Office Action on the merits according to 37 C.F.R. §1.97(b)(3). In accordance with 37 C.F.R. §1.98(a)(2), copies of each document or other information listed on the enclosed Form 1449 are provided.

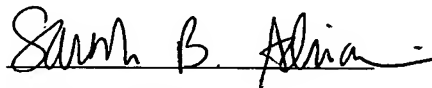
No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the reference(s) are not "prior art." Moreover, Applicants do not represent that the

references have been thoroughly reviewed or that any relevance of any portion of a reference is intended.

Consideration of the items listed is respectfully requested. Pursuant to the provisions of M.P.E.P. § 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

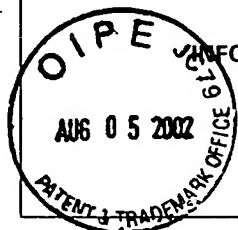
No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee, or credit any overpayment, to Deposit Account No. 50-0306.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Sarah B. Adriano", is written over a horizontal line.

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FORM 1449*



INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION

(Use several sheets if necessary)

Docket Number

D0136NP/30436.58USU1

Application Number

10/057,288

Applicant

Christian P. Larsen et al.

Filing Date

January 25, 2002

Group Art Unit

1646

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	4,603,102 (Exhibit 1)	07/29/86	Himmelman et al.			06/26/85
	5,430,057 (Exhibit 2)	07/04/95	Andersson et al.			09/30/93
	5,434,131 (Exhibit 3)	07/18/95	Linsley et al.			05/26/93
	5,559,148 (Exhibit 4)	09/24/96	Andersson et al.			05/24/95
	5,637,481 (Exhibit 5)	06/10/97	Ledbetter et al.			09/13/93
	5,773,253 (Exhibit 6)	06/30/98	Linsley et al.			07/21/95
	5,844,095 (Exhibit 7)	12/01/98	Linsley et al.			01/18/95
	5,851,795 (Exhibit 8)	12/22/98	Linsley et al.			06/02/95
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	5,885,579 (Exhibit 10)	03/23/99	Linsley et al.			07/08/97
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	6,217,867 B1 (Exhibit 14)	04/17/01	Ildstad			10/22/98

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
	WO96/23071 (Exhibit 15)	08/01/96	PCT				X

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	Abrams, Judith R. et al., "Blockade of T Lymphocyte Costimulation with Cytotoxic T Lymphocyte-associated Antigen 4-Immunoglobulin (CTLA4Ig) Reverse the Cellular Pathology of Psoriatic plaques, Including the Activation of Keratinocytes, Dendritic Cells, and Endothelial Cells," <i>Journal of Experimental Medicine</i> , 2000, 192:681-693 (Exhibit 16)
	Adams, Andrew B. et al., "Costimulation Blockade, Busulfan, and Bone Marrow Promote Titratable Macrochimerism, Induce Transplantation Tolerance, and Correct Genetic Hemoglobinopathies with Minimal Myelosuppression," <i>Journal of Immunology</i> , 2001, 167:1103-11 (Exhibit 17)
	Ahmed, Rafi et al., "Selection of Genetic Variants of Lymphocytic Choriomeningitis Virus in Spleens of Persistently Infected Mice," <i>Journal of Experimental Medicine</i> , 1984, 160:521-40 (Exhibit 18)


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*Substitute Disclosure Statement Form (PTO-1449)

Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


FORM 1449*  INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION (Use several sheets if necessary)	Docket Number D0136NP/30436.58USU1	Application Number 10/057,288
	Applicant Christian P. Larsen et al.	
	Filing Date January 25, 2002	Group Art Unit 1646

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)		
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		Aruffo, S., Presentation of "Approaches to Immune Regulation" at BIO 2000 in Boston, Massachusetts, March 27, 2000 (Exhibit 20)
		Basch, Ross S. et al., "Growth of Human Hematopoietic Cells in Immunodeficient Mice Conditioned with Cyclophosphamide and Busulfan," <i>Stem Cells</i> , 1997, 15:314-23 (Exhibit 21)
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		Bill, Jerome et al., "The MHC Molecule I-E is Necessary but not Sufficient for the Clonal Deletion of Vβ11-Bearing T Cells," <i>Journal of Experimental Medicine</i> , 1989, 169:1405-19 (Exhibit 24)
		Billingham, R. E. et al., "'Actively Acquired Tolerance' of Foreign Cells," <i>Nature</i> , 1953, 172:603-6 (Exhibit 25)
		Bratton, Donna L. et al., "Appearance of Phosphatidylserine on Apoptotic Cells Requires Calcium-mediated Nonspecific Flip-Flop and Is Enhanced by Loss of the Aminophospholipid Translocase," <i>Journal of Biological Chemistry</i> , 1997, 272:26159-65 (Exhibit 26)
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		Christian, John A. et al., "Methodologic considerations for the use of canine in vivo aged biotinylated erythrocytes to study RBC senescence," <i>Experimental Hematology</i> , 1996, 24:82-8 (Exhibit 31)
		Closse, Christèle et al., "Phosphatidylserine-related adhesion of human erythrocytes to vascular endothelium," <i>British Journal of Hematology</i> , 1999, 107:300-2 (Exhibit 32)
		Craddock, Charles, "Nonmyeloablative stem cell transplants," <i>Current Opinion in Hematology</i> , 1999, 6:383-7 (Exhibit 33)
		Dariavach, Piona et al., "Human Ig superfamily CTLA-4 gene: chromosomal localization and identity of protein sequence between murine and human CTLA-4 cytoplasmic domains," <i>European Journal of Immunology</i> , 1988, 18:1901-5 (Exhibit 34)

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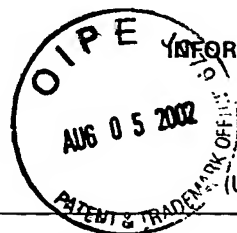
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		Dyson, P. J. et al., "Genes encoding ligands for deletion of Vβ11 T cells cosegregate with mammary tumour virus genomes," <i>Nature</i> , 1991, 349:531-2 (Exhibit 37)
		Falk, Kirsten et al., "Both Human and Mouse Cells Expressing H-2K ^b and Ovalbumin Process the Same Peptide, SIINFEKL," <i>Cellular Immunology</i> , 1993, 150:447-52 (Exhibit 38)
		Flesher, Alan R., Presentation of 'Transgenic Production, A Comparative Study' at Bio 99 in Seattle, Washington, April 15, 1999 (Exhibit 39)
		Frasch, S. Courtney et al., "Regulation of Phospholipid Scramblase Activity during Apoptosis and Cell Activation by Protein Kinase Cδ," <i>Journal of Biological Chemistry</i> , 2000, 275:23065-73 (Exhibit 40)
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		Greve, Kimberly F., "Capillary electrophoretic examination of underivatized oligosaccharide mixtures released from immunoglobulin G antibodies and CTLA4lg fusion protein," <i>Journal of Chromatography</i> , 1996, 749:237-245 (Exhibit 45)
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		Hansen, John A. et al., "Monoclonal Antibodies Identifying a Novel T-Cell Antigen and Ia Antigens of Human Lymphocytes," <i>Immunogenetics</i> , 1980, 10:247-60 (Exhibit 47)
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		Honey, Karen et al., "CD40 Ligand Blockade Induces CD4 ⁺ T Cell Tolerance and Linked Suppression," <i>Journal of Immunology</i> , 1999, 163:4805-10 (Exhibit 49)
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FORM 1449*



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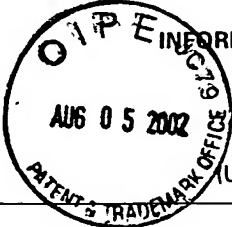
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	Krishnamurti, Lashmanan et al., "Bone Marrow Transplantation without Myeloablation for Sickle Cell Disease," <i>New England Journal of Medicine</i> , 2001, 344:68 (Exhibit 58)
	Kuypers, Frans A. et al., "Detection of Altered Membrane Phospholipid Asymmetry in Subpopulations of Human Red Blood Cells Using Fluorescently Labeled Annexin V," <i>Blood</i> , 1996, 87:1179-87 (Exhibit 59)
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	Larsen, Christian P. et al., Abstract of "Prolongation of Renal Allograft Survival with Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-IG Fusion Protein In Non-Human Primates," in <i>Transplantation</i> , 2000, 69:S123, #45 (Exhibit 62)
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OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

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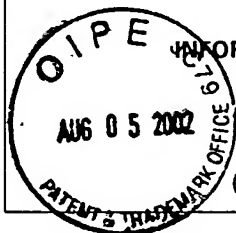
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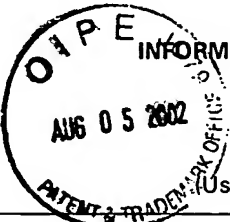
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	Applicant Christian P. Larsen et al.	
	Filing Date January 25, 2002	Group Art Unit 1646

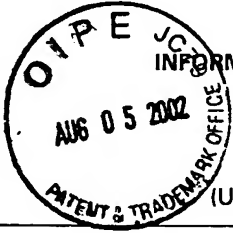
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